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Vitamin D Deficiency in Pregnant Women and Their Infants

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What is already known on this topic

Vitamin D deficiency is a serious health problem although the improvement in socio-economic status in Turkey. A new vitamin D support program has been launched for pregnant women by Ministry of Health in 2011.

What this study adds

Although vitamin D support program has been launched for pregnant women by Ministry of Health, vitamin D deficiency in pregnant women and their infants is still a serious health problem in Turkey.

ABSTRACT

Objective: Vitamin D deficiency is a serious health problem although the improvement in socio-economic status in Turkey. The aim of this study was to evaluate the maternal vitamin D status and their effect on neonatal vitamin D status after support program for pregnant women and to detect risk factors for vitamin D deficiency in Bağcılar region in İstanbul.
Methods: A total of 97 pregnant women and 90 infants were included in this study between January and October 2016. The demographic data, risk factors and daily vitamin intake were recorded. We measured serum levels of vitamin D, calcium, phosphorus and alkaline phosphatase in mothers and their infants. The relationship between their vitamin D levels and risk factors was analyzed.

Results: The mean vitamin D level for all women and all infants were found as 14.82 ±11.45 ng/ml and 13.16 ± 7.16 ng/ml, respectively. The number of mothers and infants were significantly higher in deficient group, and their mean vitamin D levels significantly lower (9.02 ± 1.34 ng/ml and 8.80 ± 1.06 ng/ml, respectively) ($p < 0.001$, $p < 0.001$). The percent of pregnant women who have received 1000-1200 IU/day of vitamin D was only found as 14.4%. When the mother groups were evaluated in terms of risk factors, there were statistically differences in daily vitamin intake and clothing style ($p < 0.001$, $p < 0.001$).

Conclusion: Vitamin D deficiency in pregnant women and their infants is still a serious health problem in Turkey, although vitamin D support program has been launched for pregnant women.

Keywords: Vitamin D, Neonate, Pregnancy

INTRODUCTION

Vitamin D is not only a lipid-soluble vitamin, but also a steroid hormone that can be synthesized endogenously. It has an important role in calcium-phosphorus homeostasis and its deficiency causes rickets in children and osteomalacia in adults (1,2). Vitamin D deficiency also may result in impairment of immune system, cancer, cardiovascular disease, diabetes, rheumatic disease, muscle weakness, chronic pain, neuropsychiatric

dysfunction (3-7). The lack of vitamin D during pregnancy is the most important risk factor for rickets in infants, also it may result in poor fetal growth and neonatal development (8-11). In addition, its deficiency in pregnant women may cause gestational diabetes mellitus and preeclampsia (12,13,).
Vitamin D deficiency is a serious health problem although the improvement in socio-economic status in Turkey. In 2005, "Vitamin D prophylaxis augmentation program" was initiated by Turkish Pediatric Endocrine Society and Ministry of Health for prevention of rickets. This program has included free distribution of supplements to provide 400 IU/day of vitamin D. At the end of this program, the prevalence of rickets decreased in children under 3 years of age (14). After this success, a new vitamin D support program has been launched for pregnant women by Ministry of Health in 2011. This program included 1200 IU vitamin D replacement to all pregnant women from 1.st trimester to 6 months after delivery (15).
The aim of this study was to evaluate the maternal vitamin D status and their effect on neonatal vitamin D status after support program for pregnant women and to detect risk factors for vitamin D deficiency in Bağcılar where is a low socio-economic region in Istanbul.

METHODS
This prospective study was conducted in cooperation with Department of Pediatrics and Department of Obstetrics and Gynecology in Medicine Hospital/ Biruni University. The study protocol was approved by the ethics committee of university and informed consent was obtained for pregnant women and their infants.

One hundred twenty pregnant women in the 3th trimester and infants were considered to include in this study but 23 women excluded from the study as they rejected inclusion of their babies. Also, 7 infants were excluded from this study because they did not have enough blood samples. The age that younger than 20 or over 40 years old, chronic disease, taking medications and twin pregnancy were accepted as exclusion criteria for mothers. Small for gestational age (<2500 g, SGA), prematurity, congenital disease or malformation, older than 28 days of age and refusal of parental consent were accepted as exclusion criteria for infants. Thus, a total of 97 pregnant women and 90 infants were included in this study between January and October 2016. Information of the mothers and their infants such as age, gender, weight, height, number of parity, socio-economic status, daily sun exposure, daily vitamin D intake, covered style of clothing and season were recorded. The mothers who were not exposed to sunlight daily were accepted as low sun exposure. Using headscarf and clothes which cover arms and legs were accepted as covered clothing style. The mothers divided into three groups according to daily vitamin D intake; none, 400-600 IU/day of vitamin D and 1000-1200 vitamin D IU/day.

Body mass index (BMI) was calculated by the formula (weight (kg)/height $(m)^2$). Blood samples for calcium (Ca), phosphorus (P), alkaline phosphatase (ALP) and 25(OH)D were taken from the mothers within 1 month before delivery and from the infants within 1 week after delivery. Samples were studied on the same day. The 25(OH)D levels were measured by enzyme linked fluorescent assay on the Mini Vidas (Biomerieux, France). Ca, P, alkaline phosphatase (ALP) were measured using the photometry method on the Cobas Integra 400 Plus (Roche Diagnostics, Germany). Participants were divided into 3 groups as deficient, insufficient, sufficient according to their vitamin D levels. 25(OH)D levels were defined that >20 ng/ml (>50 nmol/l) as sufficient, 12-20 ng/ml (30-50 nmol/l) as insufficiency, <12 ng/ml (30 nmol/l) as deficiency (16).

In this study, IBM SPSS 20 and R were used to conduct the analysis. "Statistical G Power program was used to calculate sample size. We estimated a minimum total sample size of 84 to achieve an effect size of 0.35, the power of 0.8 and Type 1 error of 0.05." Descriptive statistics are given via tables. Chi-Square Test of Independence was used to detect the significant relationships between nominal variables. To test the differences between means, t-test, one-way ANOVA for normal data and Mann-Whitney U test, Kruskal Wallis H test for non-normal data were used. To detect from which groups the difference originated, Tukey's HSD and Dunn's tests were used.

RESULTS

Ninety seven pregnant women were included in this prospective study. The mean vitamin D level for all women was found as 14.82 ±11.45 ng/ml. When the risk factors were evaluated in pregnant women, there were statistically differences in BMI, daily vitamin intake and clothing style ($p= 0.02$, $p < 0.001$, $p= 0.02$). The characteristics of the groups are shown in Table 1.

The number of women were significantly higher in deficient group ($p < 0.001$), and their mean vitamin D level significantly lower (9.02 ± 1.34 ng/ml) than insufficient (15.13 ± 2.34 ng/ml) and sufficient groups (33.95 ± 20.71 ng/ml), ($p= 0.00$). No statistically differences were found between groups in terms of Ca, P, ALP levels ($p= 0.07$ $p= 0.10$**,** $p= 0.94$) (Table 2). When the groups were evaluated in terms of risk factors, there were statistically differences in daily vitamin intake and clothing style ($p < 0.001$, $p < 0.001$).

Ninety infants were included in this prospective study. The mean vitamin D level was found as 13.16 ± 7.16 ng/ml for all infants. The mean gestational age and birth weight of infants were found as 38.45 ± 1.10 weeks and 3.36 ± 0.39 kg. The number of female infants were 48 (53%) and number of male infants were 42 (47%). Infants were divided into 3 groups according to their vitamin D levels. The number of infants in deficient group were significantly higher than insufficient and sufficient group ($p < 0.001$). The mean vitamin D level in deficient group were found as 8.80 ± 1.06 ng/ml and this level was significantly lower than insufficient and sufficient groups ($p < 0.001$). Among the groups, there were no differences in Ca, P, ALP levels (Table 3).

When the effect of maternal risk factors on their infants' vitamin D levels were evaluated, there were no statistically difference except than daily vitamin D intake. The means of vitamin D level of babies whose mothers are covered and uncovered are found as 13.01 and 13.44 ng/ml, respectively. But this difference is statistically insignificant (Independent sample T-test, p= 0.79). The means of vitamin D level of babies whose mothers took daily vitamin D none, 400-<1000 IU and 1000-1200 IU are found as 12.13, 12.95 and 16.25 ng/ml, respectively. There is a statistically significant difference in the mean values of these 3 groups (Kruskal-Wallis H test, p= 0.04), and this difference is originated from 400-<1000 IU and 1000-1200 IU groups (Dunn's test, p= 0.01).

Also, we evaluated the infants according to mother's vitamin D status. The mean vitamin D level in the infants of mothers who have deficient, insufficient and sufficient vitamin D levels were found as 10.05 ± 3.70 ng/ml, 13.06 ± 4.09 ng/ml and 24.28 ± 10.33 ng/ml, respectively ($p < 0.001$) (Table 4). The Pearson correlation between the mothers' and their babies' vitamin D levels was found significant ($p < 0.001$) and the correlation coefficient is 0.63.

DISCUSSION

Vitamin D deficiency leads to important health problems not only in mothers but also in their infants, because the vitamin D store of mother is the major source of vitamin D for fetus (9). Vitamin D amount that The World Health Organization (WHO) recommended nutrient intake (RNI) for pregnant women is 200 IU/day (17). Institute of Medicine (IOM) suggested that Estimated Average Requirement (EAR) and Recommended Dietary Allowance (RDA) for pregnant women to be 400 and 600 IU/day, respectively (18). Recent studies reported that daily dose for pregnant women should be greater 1000 IU/day to achieve adequate level (8,19). The safety dose during pregnancy is not clear, but Hollis et al. showed that Vitamin D supplementation of 4,000 IU/day for achieving adequate level was safe and effective in pregnant women (20).

International Association of Endocrinology defined the vitamin D level of 21-29 ng /ml for insufficiency and <20 ng/ml for deficiency in adults (21). However, the levels of vitamin D insufficiency and deficiency are not clearly defined and the discussion about the prevalence vitamin D deficiency is ongoing (22, 23). The recommended value for serum vitamin D level is lower in children than adults. The Endocrine Society suggests a vitamin D level of > 20 ng/ml for sufficiency, 12-20 ng/ml for insufficiency and <12 ng/ml as a lower limit for vitamin D deficiency (16). This recommendation were used in our study.

The studies which have been reported from different countries have shown its prevalence in the pregnant women and infants ranged from 4 to 60% and from 3 to 86%, respectively (24,25). In a study from Egypt, El Koumi et al. reported that only 35.8% of pregnant women had over 20 ng/ml (26). In a study from Indian, it has been reported that 84% of pregnant women had vitamin D concentrations <22.5 ng/ml (27). In a study of national survey from Belgium, vitamin D insufficiency (<30 ng/ml) and deficiency (<20 ng/ml) were found as 74.1% and 44.6% (28).

The previous studies shown that vitamin D deficiency is common in pregnant women in Turkey (29-33). In 1998, Alagöl et al. found that vitamin D levels were low in 66.6% of women of reproductive age in Istanbul (29). In 2003, Pehlivan et al. reported that 94.8% of the mothers and 24.6% of their infants had a below 16 ng/ml (30). In another study by performed Ergür et al., 18.6% of the mothers and 2.9% of the neonates had normal vitamin D levels (31). In 2008, Halicioglu et al. found that 50.4% of pregnant women had ≤10 ng/ml vitamin D concentration in İzmir where was a sunny region of Turkey (32). In a recent study conducted in Ankara in 2010, vitamin D deficiency (≤20 ng/ml) in pregnant women and their infants were found as 62.6% and 58.6%, respectively (33). In our study, the mean vitamin D level was measured as 14.82 ±11.45 ng/ml in pregnant women and 13.16 ± 7.16 ng /ml in their infants. Vitamin D deficiency in mother and infants were found as 49.5% and 56.7%, respectively. All of these data confirm that vitamin D deficiency continues to be a problem in pregnant women and their infants in Turkey.

Although The Health of Ministry has recommended 1200 IU/day, we found that the 12.4% of mother never used vitamin D supplements and the 73.2% of mother used irregular or low dose.

The percent of pregnant women who have received 1000-1200 IU/day of vitamin D was only found as 14.4% and this low value was statistically significant. When the mean vitamin D levels were compared to each other,

the level of mothers' who used low dose vitamin D supplements was significantly lower than mothers' who used recommended dose. This results show that high dose of vitamin D support is necessary and the support program should be continued.

Limited sun exposure, regular use of sunscreens, northern latitudes, dark skin, obesity, extensive clothing cover, aging, low nutritional status, malabsorption syndromes and medications have been reported as the risk factors for vitamin D deficiency (1,19). In previous studies in Turkey, winter season, low socioeconomic status, low educational status and covered clothing style were risk factors for vitamin D deficiency in mothers (31,34,35). However, Pehlivan et al. found no significant difference except covered clothing (30). Similarly, Halicioglu et al. and Cuhaci-Cakir et al. reported that covered clothing style was a risk factor for vitamin D deficiency (32,36). In this study, the difference was not in terms of socioeconomic status and season because all mothers had low or moderate incomes and number of mothers who were giving birth in winter were only 5 (5.2%). We found no differences in terms of number of parity and sunlight exposure, but vitamin D levels of mothers who had covered clothing were significantly lower than uncovered. These findings show that covered clothing style is an important factor for vitamin D deficiency in pregnant women in Turkey.

When we evaluated the infants according to vitamin D levels of their mothers, we found no difference between groups in terms of gender, gestational age, birth weight, delivery route and the levels of CA, P, ALP. However, the infants of mothers in sufficient group had significantly higher vitamin D level than other infants. The previous studies showed a strong correlation between maternal and neonatal levels of vitamin D (8,9). Ergur et al. suggested that maternal deficiency was the most important factor for vitamin D deficiency in newborns (31). Andiran et al. reported that the most important risk factor for low level in the newborn was a maternal 25OHD level below 10 ng/ml (35). Similarly, we found a positive strong correlation between the mothers' and their babies' vitamin D levels and low level of vitamin D in mother was an important risk factor for deficiency in infants.

When we evaluated relationship between infants' Vitamin D level and their mothers' clothing style together with daily vitamin D intake, we found that there were no significant differences in the aspect of mothers clothing style. However, mothers' low vitamin intake was found as a risk factor for infants' Vitamin D level.

Our study have some limitations that should be mentioned. First, this study was carried out in a region of Istanbul and second, this region has a low socio-economic level. Therefore, this study may be insufficient to evaluate all socio-economic levels and the other regions in Turkey. Further studies are needed to evaluate the limitations of this study.

In conclusion, although vitamin D support program has been launched for pregnant women by Ministry of Health, vitamin D deficiency in pregnant women and their infants is still a serious health problem in Turkey. Also, the data in this study indicate that the usage rate of the recommended dose in support program was very low and the prescribed supplements were generally multivitamin preparations. Therefore, the support program should be continued and physicians should be more informed about the content of support program in pregnancy.

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TABLES

Table 1. Serum 25(OH)D Levels in Pregnant Women According to Their Characteristics.

	n (%)	25(OH)D levels (ng/ml) (mean±SD)	p value
All pregnant women	97 (100%)	14.82 ±11.45	
Age 20-30 >=30	 51 (52.6%) 46 (47.4%)	 15.41 ± 11.79 14.17 ± 11.16	 [1]0.60
BMI (kg/m^2) <18.5 18.5-24.9 25-29.9 ≥30	 3 (3.1%) 56 (57.7%) 26 (26.8%) 12 (12.4 %)	 8.10 ± 0.25 15.82 ± 11.42 14.62 ± 14.15 12.3 ± 3.68	 [2]0.02*
Number of Parity 1 2 ≥3	 37 (38.1%) 37 (38.1%) 23 (23.8%)	 14.38 ± 5.8 15.19 ± 12.71 14.95 ± 15.88	 [3]0.83
Socio-economic status Low Moderate	 45 (46.4%) 52 (53.6%)	 15.28 ± 12.37 14.42 ± 10.7	 [1]0.71
Leukocyte	 12 (12.4%) 71 (73.2%) 14 (14.4%)	 11.44 ± 5.27 12.49 ± 4.75 29.56 ± 23.43	 [3] <0.001**
Hematocrit	 41 (42.3%) 56 (57.7%)	 15.13 ± 11.05 14.41 ± 12.10	 [1]0.76
Hemoglobin	 65 (67%) 32 (33%)	 12.96 ± 6.71 18.61 ± 17.06	 [1]0.02*
MCV	 5 (5.2%) 55 (56.6%) 35 (36.1%) 2 (2.1%)	 13.45 ± 5.07 14.68 ± 10.97 15.07 ± 13.2 18.02 ± 5.63	 [2]0.56
One-way Analysis of Variance,			

Table 2. Maternal groups and their laboratory results according to Vitamin D status.

	Deficient	Insufficient	Sufficient	p
Number of women (n, %)	48 (49.5%)	35 (36.1%)	14 (14.4%)	[1] <0.001**

25 (OH) D(ng/ml) (mean±SD)	9.02 ± 1.34	15.13 ± 2.34	33.95 ± 20.71	[2] <0.001**
Ca (mg/dl) (mean±SD)	8.84 ± 0.53	9.06 ± 0.45	9.07 ± 0.59	[2]0.07
P (mg/dl) (mean±SD)	3.67 ± 0.68	3.89 ± 0.45	3.90 ± 0.71	[2]0.10
ALP (U/L) (mean±SD)	140.71 ± 50.07	142.81 ± 45.63	138.00 ± 22.75	[2]0.94
**: Statistically significant at 0.05, **: Statistically significant at 0.01, 1: Chi-Square test of Indepence, 2: One-way Analysis of Variance.*				

Table 3. Infant groups and their laboratory results according to Vitamin D status.

	Deficient	Insufficient	Sufficient	p
Number of infants (n, %)	51 (56.7%)	29 (32.2%)	10 (11,1%)	[1] <0.001**
25 (OH) D(ng/ml) (mean±SD)	8.80 ± 1.06	15.43 ± 2.33	28.84 ± 9.26	[2] <0.001**
Ca (mg/dl) (mean±SD)	10.66 ± 5.67	9.86 ± 1.24	10.06 ± 0.64	[2]0.49
P (mg/dl) (mean±SD)	5.74 ± 0.63	5.61 ± 0.78	5.81 ± 0.63	[2]0.85
ALP (U/L) (mean±SD)	185.53 ± 50.76	192.48 ± 52.11	166.30 ± 43.95	[2]0.57
**: Statistically significant at 0.05, **: Statistically significant at 0.01* *: One-way Analysis of Variance.*				

Table 4. The number of infants and their vitamin D status according to maternal groups.

	The number of infants and their vitamin D status		
Maternal Groups	n (%)	25 (OH)D levels (ng/ml) ± SD	p
Sufficient	13 (14.5%)	24.28 ± 10.33	[1] <0.001**
Insufficient	29 (32.2%)	13.06 ± 4.09	
Deficient	48 (53.3%)	10.05 ± 3.70	
Total	90 (100%)	13.08 ± 7.16	
: One-way Analysis of Variance			